

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



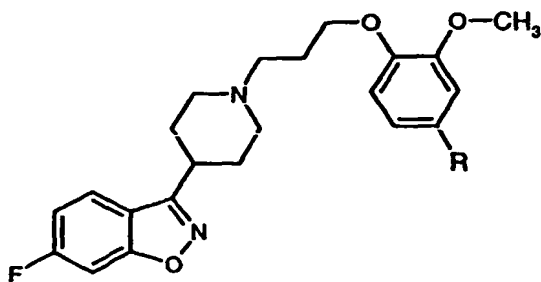
(43) International Publication Date
22 January 2004 (22.01.2004)

PCT

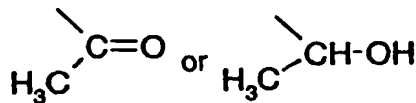
(10) International Publication Number
WO 2004/006886 A2

- (51) International Patent Classification⁷: **A61K 9/00**
- (21) International Application Number:
PCT/EP2003/007619
- (22) International Filing Date: 14 July 2003 (14.07.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
0216416.8 15 July 2002 (15.07.2002) GB
- (71) Applicant (for all designated States except AT, US): **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).
- (71) Applicant (for AT only): **NOVARTIS PHARMA GMBH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **WIECKHUSEN, Dierk** [DE/DE]; Mühlenstrasse 78, 79589 Binzen (DE). **GLAUSCH, Alexandra** [DE/DE]; Schutzackerstrasse 20, 79576 Weil am Rhein (DE). **AHLHEIM, Markus** [DE/DE]; Gewerbestrasse 9, 79219 Staufen (DE).
- (74) Agent: **GRUBB, Philip**; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SY, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INJECTABLE DEPOT FORMULATION COMPRISING CRYSTALS OF ILOPERIDONE



(I)



(II)

(57) Abstract: An injectable depot formulation comprising crystals having Structure (I) wherein R is (FII) and the X₅₀ value of the crystals is from 1 to 200 microns. Depot formulations containing crystals of iloperidone or its metabolite have the following advantages: (i) release of the crystals in plasma can be correlated with the size of the crystals; (ii) absorption of the crystals in plasma can be correlated with the size of the crystals; (iii) the particle size of the crystals can be controlled by crystal engineering and/or milling; and (iv) the crystals are stable upon storage, and stable to sterilization procedures, such as gamma irradiation.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



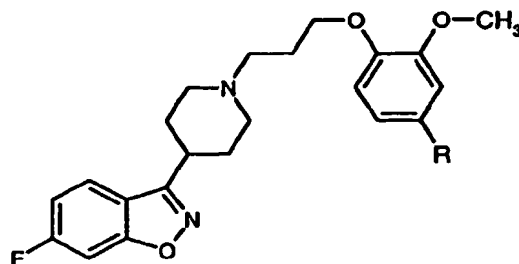
(43) International Publication Date
22 January 2004 (22.01.2004)

PCT

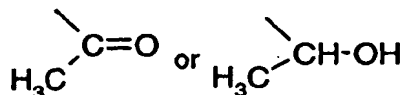
(10) International Publication Number
WO 2004/006886 A3

- (51) International Patent Classification⁷: **A61K 47/38**, 47/10, 47/26, 31/454
- (21) International Application Number: PCT/EP2003/007619
- (22) International Filing Date: 14 July 2003 (14.07.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
0216416.8 15 July 2002 (15.07.2002) GB
- (71) Applicant (for all designated States except AT, US): **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).
- (71) Applicant (for AT only): **NOVARTIS PHARMA GMBH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).
- (72) Inventors; and
(75) Inventors/Applicants (for US only): **WIECKHUSEN, Dierk** [DE/DE]; Mühlenstrasse 78, 79589 Binzen (DE). **GLAUSCH, Alexandra** [DE/DE]; Schutzackerstrasse 20, 79576 Weil am Rhein (DE). **AHLHEIM, Markus** [DE/DE]; Gewerbestrasse 9, 79219 Staufen (DE).
- (74) Agent: **GRUBB, Philip**; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SY, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- (88) Date of publication of the international search report: 19 February 2004
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INJECTABLE DEPOT FORMULATION COMPRISING CRYSTALS OF ILOPERIDONE



(I)



(FII)

(57) Abstract: An injectable depot formulation comprising crystals having Structure (I) wherein R is (FII) and the X_{50} value of the crystals is from 1 to 200 microns. Depot formulations containing crystals of iloperidone or its metabolite have the following advantages: (i) release of the crystals in plasma can be correlated with the size of the crystals; (ii) absorption of the crystals in plasma can be correlated with the size of the crystals; (iii) the particle size of the crystals can be controlled by crystal engineering and/or milling; and (iv) the crystals are stable upon storage, and stable to sterilization procedures, such as gamma irradiation.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/07619

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K47/38 A61K47/10 A61K47/26 A61K31/454

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KELLEHER, JAMES P.; ET AL.: "Advances in atypical antipsychotics for the treatment of schizophrenia. New formulations and new agents." CNS DRUGS, vol. 16, no. 4, 2002, pages 249-261, XP001079584 the whole document ---	1-25
A	EP 0 402 644 A (HOECHST-ROUSSEL) 19 December 1990 (1990-12-19) the whole document ---	1-25
P, A	WO 03 020707 A (NOVARTIS) 13 March 2003 (2003-03-13) the whole document -----	1-25

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

30 December 2003

Date of mailing of the international search report

08/01/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Ventura Amat, A

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP/03/07619

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 402644	A	19-12-1990	AT 126512 T 15-09-1995
		AU 640653 B2 02-09-1993	
		AU 5577090 A 22-11-1990	
		CA 2017193 A1 19-11-1990	
		CN 1305812 A 01-08-2001	
		CN 1048037 A ,B 26-12-1990	
		CZ 9002425 A3 12-03-1997	
		DE 69021645 D1 21-09-1995	
		DE 69021645 T2 22-02-1996	
		DK 402644 T3 02-01-1996	
		EP 0402644 A1 19-12-1990	
		ES 2076253 T3 01-11-1995	
		FI 104072 B1 15-11-1999	
		FI 991869 A 02-09-1999	
		GR 3017447 T3 31-12-1995	
		HK 1006710 A1 12-03-1999	
		HU 58720 A2 30-03-1992	
		HU 9500576 A3 28-12-1995	
		IE 68431 B1 12-06-1996	
		IL 94425 A 27-02-1994	
		JP 1931594 C 12-05-1995	
		JP 3063263 A 19-03-1991	
		JP 6062580 B 17-08-1994	
		KR 157308 B1 16-11-1998	
		NO 902214 A ,B, 20-11-1990	
		NZ 233710 A 26-05-1992	
		PH 30431 A 09-05-1997	
		PL 285247 A1 11-02-1991	
		PT 94084 A ,B 08-01-1991	
		RU 2147583 C1 20-04-2000	
		SK 242590 A3 04-11-1998	
		RU 2062776 C1 27-06-1996	
		US RE37029 E1 23-01-2001	
		US RE37478 E1 18-12-2001	
		US RE37729 E1 04-06-2002	
		US 5658911 A 19-08-1997	
		US 5776963 A 07-07-1998	
		US 5550130 A 27-08-1996	
		US 5629326 A 13-05-1997	
		US 5977140 A 02-11-1999	
		US 5977113 A 02-11-1999	
		US 5552414 A 03-09-1996	
		US 5612342 A 18-03-1997	
		US 6001834 A 14-12-1999	
		US 5559117 A 24-09-1996	
		US 5574032 A 12-11-1996	
		US 5648363 A 15-07-1997	
		US 5624927 A 29-04-1997	
		US 5607945 A 04-03-1997	
		US 5583145 A 10-12-1996	
WO 03020707	A	13-03-2003	WO 03020707 A1 13-03-2003